



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Mitchell A. Avery
Appl. No.: 09/981,312
Filed: October 15, 2001
Docket No.: 1786
Conf. No. 4970
Title: **SYNTHESIS OF EPOTHILONES AND RELATED ANALOGS**

Art Unit: (1614)
Examiner: Andrea D. Souza Small

Action: **TRANSMITTAL OF INFORMATION DISCLOSURE**
Date: April 22, 2003

TO: Assistant Commissioner for Patents
Washington, DC 20231

Sir:

The documents identified on the attached forms PTO/SB/08 have come to the attention of the undersigned in connection with the subject application. Unless otherwise indicated, copies of these documents are attached, and it is respectfully requested that they be made of record in this proceeding. The identification of these documents is for the purpose of meeting Applicant's duty of disclosure under 37 C.F.R. §1.56 and is not intended to be an admission that any of these documents constitute prior art as to the invention disclosed and claimed in the subject application. Further, Applicant makes no representation whether any of these references qualify as prior art under 35 U.S.C. § 102.

In addition, Applicant has a general awareness of various patent and non-patent references that have not been listed in the attached forms. Although Applicant is generally aware of these references, he cannot attest to any particular relevance each reference may have to the patentability to the invention disclosed and claimed in the subject

application. Copies of these references were either unable to be located, or in a foreign language and are as follows:

- Schinzer, D.; Bauer, A.; Bohm, O.M.; Limberg, A.; Cordes, M. *Total Synthesis of (-)-epothilone A*. Chemistry--A European Journal 1999, Vol. 5, Pages 2483-2491.
- Nicolaou, K.C.; King, N.P.; Finlay, M.R.V.; He, Y.; Roschangar, F.; Vourloumis, D.; Vallberg, H.; Sarabia, F.; Ninkovic, S.; Hepworth, D. *Total synthesis of epothilone E and related side-chain modified analogues via a Stille coupling based strategy*. Bioorganic & Medicinal Chemistry 1999, Vol. 7 Pages 665-697.
- Nicolaou, K.C.; King, N.P.; He, Y. *Ring-closing metathesis in the synthesis of epothilones and polyether natural products*. Topics in Organometallic Chemistry 1998, Vol. 1 Pages 73-104.
- Marshall, A.; Castellino, A. *Total synthesis of epothilone*. Nat. Biotechnol, 1997, Vol. 15, Page 205.
- Nicolaou, K.C.; Winssinger, N.; Pastor, J.; Ninkovic, S.; Sarabia, F.; He, Y.; Vourloumis, D.; Yang, Z.; Li, T.; Giannakakou, P.; Hamel, E. *Synthesis of epothilones A and B in solid and solution phase*. Nature (London) 1997, Vol. 387, Pages 268-272.
- Nakamura, S.; Hashimoto, S.; *Total synthesis of antitumor antibiotic epothilone having same action mechanism with taxol*. Kagaku (Kyoto), 1997, Vol. 52, Pages 70-71.
- Ashley, G.; Arslanian, R.L.; Carney, J.; Metcalf, B.; Tang, L.; *Preparation of epothilone derivatives for pharmaceutical use in the treatment of cancer and other disorders characterized by cellular hyperproliferation*. PCT Int. Appl.; (Kosan Biosciences, Inc., USA). Wo, 2002, 114 pp.
- Bandyopadhyay, R.; Malloy, T.M.; Panaggio, A.; Raghavan, K.S.; Varia, S.A. *Pharmaceutical dosage forms of epothilones for oral administration*. PCT Int. Appl.; (Bristol-Myers Squibb Company, USA). Wo, 2002, 41pp.
- Hoefle, G.; Glaser, N. *Preparation of triazolo-epothilones for pharmaceutical use as fungicides and antitumor agents*. PCT Int. Appl.; (Gesellschaft fuer Biotechnologische Forschung m.b.H. (GBF), Germany). Wo, 2002, 25 pp.

- Dimarco, J.D.; Gougoutas, J.Z.; Vitez, I.M.; Davidovich, M.; Galella, M.; Malloy, T.M.; Guo, Z.; Favreau, D. *Preparation of polymorphs of an epothilone analog and their use as antitumor agents*. PCT Int. Appl.; (Bristol-Myers Squibb Company, USA). Wo, 2002, 36 pp.
- Santi, D.V.; Ashley, G.; Myles, D.C. *Process for the biomediated preparation of intermediates for use in the synthesis of polyketides, such as epothilone D and discodermolide*. PCT Int. Appl.; (Kosan Biosciences, Inc., USA). Wo, 2002, 129 pp.
- Santi, D.; Farids, M.; Ashley, G. *Preparation of epothilone derivatives for pharmaceutical use in the treatment of cancer and other disorders characterized by cellular hyperproliferation*. PCT Int. Appl.; (Kosan Biosciences, Inc., USA). Wo, 2001, 87 pp.
- Klar, U.; Gay, J.; Skuballa, W.; Schwede, W.; Buchmann, B.; Bunte, T.; Lichtner, R. *Synthesis of radioactively labeled epothilone derivatives and their biochemical and pharmaceutical usage*. PCT Int. Appl.; (Schering Aktiengesellschaft, German). Wo, 2001, 31 pp.
- Danishefsky, S.J.; Lee, C.B.; Chappell, M.; Stachel, S.; Chou, T. -c. *Synthesis of epothilones, intermediates and analogs for use in treatment of cancers with multidrug resistant phenotype*. PCT Int. Appl.; (Sloan-Kettering Institute for Cancer Research, USA). Wo, 2001, 234 pp.
- Sinha, S.C.; Lerner, R.A.; Barbas, C.F.; Sun J. *Synthesis and biological activity of 13-alkyl epothilone derivatives*. PCT Int. Appl.; (Novartis A.-G., Switz.; Scripps Research Institute). Wo, 2001, 50 pp.
- Mulzer, J.; Martin, H. *Process for the production of epothilone B and derivatives as well as intermediate products for this process*. PCT Int. Appl.; (Schering Aktiengesellschaft, Germany). Wo, 2001 50 pp.
- Kim, S.-H.; Johnson, J.A. *A process for the reduction of oxiranyl epothilones to olefinic epothilones*. PCT Int. Appl.; (Bristol-Myers Squibb Co., USA). Wo, 2000, 19 pp.
- Klar, U.; Schwede, W.; Skuballa W.; Buchmann, B.; Hoffmann, J.; Lichtner, R. *Preparation of 6-alkynyl-, 6-alkynyl- and 6-epoxyepothilone derivatives and their antitumor activity*. PCT Int. Appl.; (Schering Aktiengesellschaft, Germany). Wo, 2000, 298 pp.

- Klar, U.; Schwede, W.; Skuballa, W.; buchmann, B.; Hofmann, J.; Lichtner, R. *6-Alkenyl and 6-alkynyl derivatives of epothilone*. Ger. Offen.; (Schering A.-G., Germany). De, 2000, 18 pp.
- Santi, D.V.; Xue, Q.; Ashley, G. *A method for preparing large libraries of polyketides and non-ribosomal peptides using combinations of plasmids carrying genes for different functional domains of the biosynthetic enzymes*. PCT Int. Appl.; (Kosan Biosciences, Inc., USA). Wo, 2000, 32 pp.
- Georg, G.I.; Nair, S.K.; Reiff, E.; Tunoorli, A.R.; Henri, J.T. *Preparation of precursors for synthesis of epothilones*. PCT Int. Appl.; (The University of Kansas, USA). Wo, 2000, 44 pp.
- Borzilleri, R.M.; Kim, S.-H.; Regueiro-Ren, A.; Vite, G. D. *Process for the preparation of aziridinyl epothilones from oxiranyl epothilones*. PCT Int. Appl.; (Bristol-Myers Squibb Co., USA). Wo, 2000, 37 pp.
- Hoefle, G.; Glaser, N.; Leibold, T.; Vite, G.; Kim, S.-h. *Preparation of C-21 modified epothilones for use as anticancer agents*. PCT Int. Appl.; (Gesellschaft fuer Biotechnologische Forschung MbH (Gbg), Germany, Bristol-Myers Squibb Co.). Wo, 2000, 106 pp.
- Klar, U.; Skuballa, W.; Buchmann, B.; Schwede, W.; Schirner, M. *Preparation of new epothilone derivatives and their use as antitumor agents*. PCT Int. Appl.; (Schering Aktiengesellschaft, Germany). Wo, 2000, 105 pp.
- Klar, U.; Skuballa, W.; Buchmann, B.; Schwede, W.; Schirner, M. *Preparation of epothilone derivatives useful as pharmaceuticals*. PCT Int. Appl.; (Schering A.-G., Germany). Wo, 2000, 141 pp.
- Li, W.; Matson, J.A.; Huang, X.; Lam, K.S.; McClure, G.A. *Microbial transformation method for the preparation of an epothilone*. PCT Int. Appl.; (Bristol-Myers Squibb Co., USA). Wo, 2000, 42 pp.
- Altmann, K.H.; Bold, G.; Caravatti, G.; Florsheimer, A. *Epothilone derivatives and their use as antitumor agents*. PCT Int. Appl.; (Novartis A.-G., Switz.; Novartis-Erfindungen Verwaltungsgesellschaft m.b.H.). Wo, 2000, 129 pp.
- Julien, B.; Katz, L.; Khosla, C.; Tang, L.; Ziermann, R. *Epothilone and epothilone derivatives production based on recombinant nucleic acids encoding the epithilone polyketide synthase from Sorangium cellulosum*. PCT Int. Appl.; (Kosan Biosciences, Inc., USA). Wo, 200, 138 pp.

- Mulzer, J.; Mantoulidis, A.; Oehler, E. *An efficient procedure for the synthesis of epothilone B, derivatives, and its intermediates*. Ger. Offen.; (Schering A.-G., Germany), De, 2000, 32 pp.
- Beyer, S.; Mueller, R.-J. *A DNA sequence encoding the genes of epothilone biosynthesis of Sorangium cellulosum*. Ger. Offen.; (Gesellschaft fuer Biotechnologische Forschung m.b.H. (GBF), Germany), De, 2000, 36 pp.
- Buchmann, B.; Klar, U.; Skuballa, W.; Schwede, W.; Schirmer, M.; Menrad, A. *The preparation process, intermediate products and pharmaceutical use of epothilone derivatives*. PCT Int. Appl.; (Schering A.-G., Germany). Wo, 2000, 86 pp.
- Vite, G.D.; Kim, S.-H.K.; Hofle, G. *Synthesis and cytotoxicity of 12,13-modified epothilone derivatives for use in treatment of tumors or other hyperproliferative cellular disease*. PCT Int. Appl.; (Bristol-Myers Squibb Company, USA). Wo, 1999, 89 pp.
- Kim, S.-H.; Johnson, J.A. *A process for the reduction of oxiranyl epothilones to olefinic epothilones*. PCT Int. Appl.; (Bristol-Myers Squibb Company, USA). Wo, 1999, 19 pp.
- Kim, S.-H.; Borzilleri, R.M. *A process for the preparation of ring-opened epothilone intermediates which are useful for the preparation of epothilone analogs*. PCT Int. Appl.; (Bristol-Myers Squibb Company, USA). Wo, 1999, 20 pp.
- Krause, W. *Coated medical implants, method for their preparation and their application for restenosis prophylaxis*. Ger.; (Schering A.-G., Germany). De, 1999, 4 pp.
- Danishefsky, S.J.; Balog, A.; Bertinato, P.; Su, D.-S.; Chou, T.-C.; Meng, D.F.; Kamenecka, T.; Sorensen, E.J. *Synthesis of epothilones, intermediates and analogs for use in treatment of cancers with multidrug-resistant phenotype*. PCT Int. Appl.; (Sloan-Kettering Institute for Cancer Research, USA). Wo, 1999, 175 pp.
- *Methods for preparation of epothilone derivatives*. Ger. Offen.; (Gesellschaft fuer Biotechnologische Forschung m.b.H. (GBF), Germany). De, 1998, 2 pp.
- Schinzer, D.; Limberg, A.; Boehm, O.M. *Intermediate products within the total synthesis of Epothilones A and B*. Ger.; (Schering A.-G., Germany). De, 1997, 14 pp.

- Hoefle, G.; Bedorf, N.; Gerth, K.; Reichenbach, H. *Epothilone derivatives*. Ger. Offen.; (Gesellschaft fuer Biotechnologische Forschung mbH (GBF), Germany). De, 1993, 10 pp.
- Klar, U.; Schwede, W.; Skuballa, W.; Buchmann, B.; Schirner, M. *Preparation of new epothilone derivatives and their pharmaceutical uses*. Ger. Offen.; (Schering A.-G., Germany). De, 2000, 74 pp.
- Hoefle, G.; Glaser, N.; Leibold, T. *Synthesis and cytotoxicity of C-21 modified epothilones*. Ger. Offen.; (Gesellschaft Fuer Biotechnologische Forschung m.b.G. (Gbf), Germany). De, 2000, 24 pp.
- Klar, U.; Schwede, W.; Buchmann, B.; Skuballa, W.; Schirner, M.; Grimm, M. *Preparation of new epothilone derivatives having pharmaceutical application as antitumor agents*. PCT Int. Appl.; (Schering Aktiengesellschaft, Germany). Wo, 2000, 70 pp.
- Klar, U.; Schwede, W.; Skuballa, W.; Buchmann, B.; Schirner, M. *Preparation of new epothilone derivatives and their pharmaceutical uses*. PCT Int. Appl.; (Schering A.-G., Germany). Wo, 2000, 54 pp.
- Hofle, G.; Glaser, N.; Leibold, T. *Preparation of epothilone A N-oxide and epothilone B N-oxide*. Eur. Pat. Appl.; (Gesellschaft fuer Biotechnologische Forschung m.b.H. (GBF), Germany). Ep, 2000, 8 pp.
- Hoefle, G.; Leibold, T. *Preparation of epothilone derivatives and their use*. PCT Int. Appl.; (Gesellschaft Fur Biotechnologische Forschung M.b.H. (gbf), Germany). Wo, 1999, 17 pp.
- Klar, U.; Schwede, W.; Skuballa, W.; Buchmann, B.; Schirner, M. *Preparation of new epothilone derivatives as pharmaceutical agents*. PCT Int. Appl.; (Schering Aktiengesellschaft, Germany). Wo, 1999, 185 pp.
- Klar, U.; Schwede, W.; Skuballa, W.; Buchmann, B.; Schirner, M. *New (C1-C6)-fragments, method for their preparation and their application for synthesis of epothilone and epothilone derivatives*. Ger. Offen.; (Schering A.-G., Germany). De, 1999, 18 pp.
- Klar, U.; Schwede, W.; Skuballa, W.; Buchmann, B.; Schirner, M. *New (C13-C15)-fragments, method for their preparation and their application for synthesis of epothilone and epothilone derivatives*. Ger. Offen.; (Schering A.-G., Germany). De, 1999, 14 pp.
- Klar, U.; Schwede, W.; Skuballa, W.; Buchmann, B.; Schirner, M. *New method for the preparation of the C(1)-C(6)-segment of epothilone and*

epothilone derivatives. Ger. Offen.; (Schering A.-G., Germany). De, 1999, 12 pp.

- Mulzer, J.; Mantoulidis, A. *Method for the production and use of thiazole derivatives*. PCT Int. Appl.; (Schering Actiengesellschaft, Germany). Wo, 1999, 33 pp.
- Mulzer, J.; Mantoulidis, A. *Method for the preparation and assembly of intermediate products in the production of epothilones*. Ger. Offen.; (Schering A.-G., Germany). De, 1998, 18 pp.
- Wessjohann, L.A.; Kalesse, M. *Preparation of prenyl derivatives as building blocks for epothilones*. Ger Offen.; (Germany). De, 1998, 8 pp.
- Hofle, G.; Sefkow, M. *Procedure for the preparation of epothilones with a modified side chain*. PCT Int. Appl.; (Gesellschaft Fur Biotechnologische Forschung m.b.H. (Gbf), Germany). Wo, 1998, 20 pp.
- Wessjohann, L.A.; Gabriel, T. *Preparation of epothilone synthon*. Ger Offen.; (Germany). De, 1998, 8 pp.
- Schinzer, D.; Limberg, A.; Bohm, O.M.; Bauer, A.; Cordes, M. *Method for producing epothilones and the intermediate products obtained during the production process*. PCT Int. Appl.; (Novartis Aktiengesellschaft, Switz.; Schinzer, Dieter; Limberg, Anja; Bohm, Oliver M.; Bauer, Armin; Cordes, Martin). Wo, 1998, 48 pp.
- Hoefle, G.; Kiffe, M. *Preparation of epothilone derivatives as agrochemicals and pharmaceuticals*. Ger. Offen.; (Gesellschaft fuer Biotechnologische Forschung Mbh (Gbf), Germany). De, 1997, 9 pp.
- Hofle, G.; Kiffe, M. *Preparation of epothilone derivatives as agrochemicals and pharmaceuticals*. PCT Int. Appl.; (Gesellschaft Fur Biotechnologische Forschung Mbh (Gbf), Germany; Hofle, Gerhard; Kiffe, Michael). Wo, 1997, 38 pp.
- Nicolaou, K.C.; Winssinger, N.; Pastor, J.; Ninkovic, S.; Sarabia, F.; He, Y.; Vourloumis, D.; Yang, Z.; Li, T.; Giannakakou, P.; Hamel, E. Synthesis of Epothilones A and B in Solid and Solution Phase [Erratum to document cited in CA127:4950] Nature (London) 1997, Vol. 390, Page 100.
- Hashem, M.A.; Jung, A.; Ries, M.; Kirschning, A. Errata and Addenda 1998, Page 195.

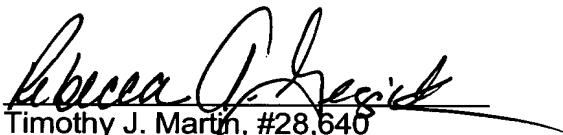
- DeBrabander, J.; Rosset, S.; Bernardinelli, G. Errata and Addenda 1997, Page 824.
- Holton, R.A.; Somoza, C.; Kim, H.-B.; Liang, F.; Biediger, R.J.; Boatman, P.D.; Shindo, M.; Smith, C.C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K.K.; Gentile, L.N.; Liu, J.H. First Total Synthesis of Taxol 1. Functionalization of the B Ring. Journal of American Chemical Society 1994, Vol. 116, Pages 1597-1598.

Please initial the attached form PTO/SB/08 where indicated and return a copy of the initialed document to the undersigned as an indication that the listed references have been considered and made of record.

The Examiner is courteously solicited to enter an expeditious allowance of this application. If any questions remain to be addressed, it is respectfully requested that the undersigned attorney for the Applicants be contacted at the number listed below.

Respectfully submitted,

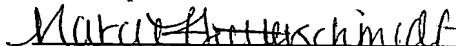
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Marcie F. Lutterschmidt